Clinical Pharmacokinetics of Alfentanil, Fentanyl and Sufentanil
An Update

Jens Scholz, Markus Steinfath and Martin Schulz
1 Department of Anaesthesiology, University of Hamburg, University Hospital Eppendorf, Hamburg, Germany
2 Drug Information Center, Federal Union of German Associations of Pharmacists (ABDA), Eschborn, Germany

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Summary

Alfentanil, fentanyl and sufentanil are synthetic opioid analgesics acting at specific opioid receptors. These opioids are widely used as analgesics to supplement general anaesthesia for various surgical procedures or as primary anaesthetic agents in very high doses during cardiac surgery. Fentanyl and sufentanil especially are administered via infusion for long term analgesia and sedation in intensive care patients.

Opioid analgesics are mainly administered using the intravenous route. However, other techniques of administration, including epidural, intrathecal, transdermal and intranasal applications, have been demonstrated.

Important pharmacokinetic differences between alfentanil, fentanyl and sufentanil have been shown in many reports. Alfentanil has the most rapid analgesic onset and time to peak effect as well as the shortest distribution and elimination half-lives. The volume of distribution and total body clearance of this agent are smaller when compared with those of fentanyl and sufentanil.

The pharmacokinetics of the opioid analgesics can be affected by several factors including patient age, plasma protein content, acid-base status and cardio-
pulmonary bypass, but not significantly by renal insufficiency or compensated hepatic dysfunction. In addition, pharmacokinetic properties can be influenced by changes in hepatic blood flow and administration of drug combinations which compete for the same plasma protein carrier or metabolising pathway.

Although comparing specific pharmacokinetic parameters such as half-lives is deeply entrenched in the literature and clinical practice, simply comparing half-lives is not a rational way to select an opioid for specific requirements. Using pharmacokinetic-pharmacodynamic models, computer simulations based on changes in the effect site opioid concentration or context-sensitive half-times seem to be extremely useful for selecting an opioid on a more rational basis.

The endogenous opioid peptides and the opioid receptors, including their subtypes which have already been cloned, constitute a complex physiological pain relieving system. Opioid receptors are coupled to guanine nucleotide-binding regulatory proteins (G proteins) which mediate cellular effects such as inhibition of adenylate cyclase, activation of potassium channels, and inhibition of voltage-dependent calcium channels, resulting in the various well known opioid-related effects.

Over the past 30 years, Paul Janssen and his associates have been extremely successful in developing a clinically relevant series of synthetic opioids specifically acting at the opioid receptors. Fentanyl, the first of the 4-anilinopiperidine series of opioid agonists (fig. 1), is a chemical congener of the reversed ester of pethidine (meperidine), and was introduced into clinical practice in the early 1960s. The more recently developed drugs, such as alfentanil (which has the shortest half-life after bolus administration) and sufentanil (the more potent), offer a greater selection for practical use (fig. 1). The major use for these synthetic opioids is to provide potent analgesia, particularly in anaesthesia, for various surgical procedures and intensive care medicine.

This article reviews the available pharmacokinetic data on alfentanil, fentanyl and sufentanil, particularly in light of the various factors affecting the pharmacokinetics of these opioid analgesics.

1. Basal Pharmacokinetic Characterisation

This section highlights the pharmacokinetic properties of alfentanil, fentanyl and sufentanil observable in patients undergoing elective surgery, or healthy volunteers without malfunction of particular organ systems. Table I summarises the pharmacokinetics and basic physicochemical variables of alfentanil, fentanyl and sufentanil by listing the analgesic onset, time to peak effect, non-ionised fraction, lipid solubility, apparent volume of distribution (Vd) after bolus administration, plasma protein binding, distribution half-life (t1/2a), elimination half-life (t1/2b) and total body clearance (CL) after bolus administration.

The pharmacokinetics of these opioid analgesics are compared with those of morphine. This contrast shows the relatively short onset and time to peak effect of alfentanil, fentanyl and sufentanil compared with morphine. The extremely high amount of non-ionised molecules of alfentanil results in a very short onset and time to peak effect because most of the drug can overcome the blood-brain barrier. The highest lipid solubility expressed as octanol/water-coefficient was found for sufentanil. The Vd, t1/2a and t1/2b of sufentanil were found between those of fentanyl and alfentanil. It is conceivable that the reduced Vd of sufentanil compared with fentanyl is, at least in part, responsible for the higher hepatic metabolism rate of sufentanil, resulting in a slightly reduced t1/2b. The plasma clearance of fentanyl and sufentanil were similar and faster when compared with alfentanil.

Alfentanil is predominantly, if not exclusively, metabolised by cytochrome P450 (CYP) 3A3/4. Fentanyl undergoes phase I metabolism, predominantly by oxidative N-dealkylation, and sufentanil is metabolised by N-dealkylation at the piperidine and amide nitrogens as well as by O-demethylation.